A SCIENTIFIC APPROACH TO PANDEMIC PREPAREDNESS

WHO R&D Blueprint Consultation
A Scientific Framework for Epidemic and Pandemic Research Preparedness
Scientific opportunities to achieve fast and equitable access to high-quality and trusted vaccines for future pandemics
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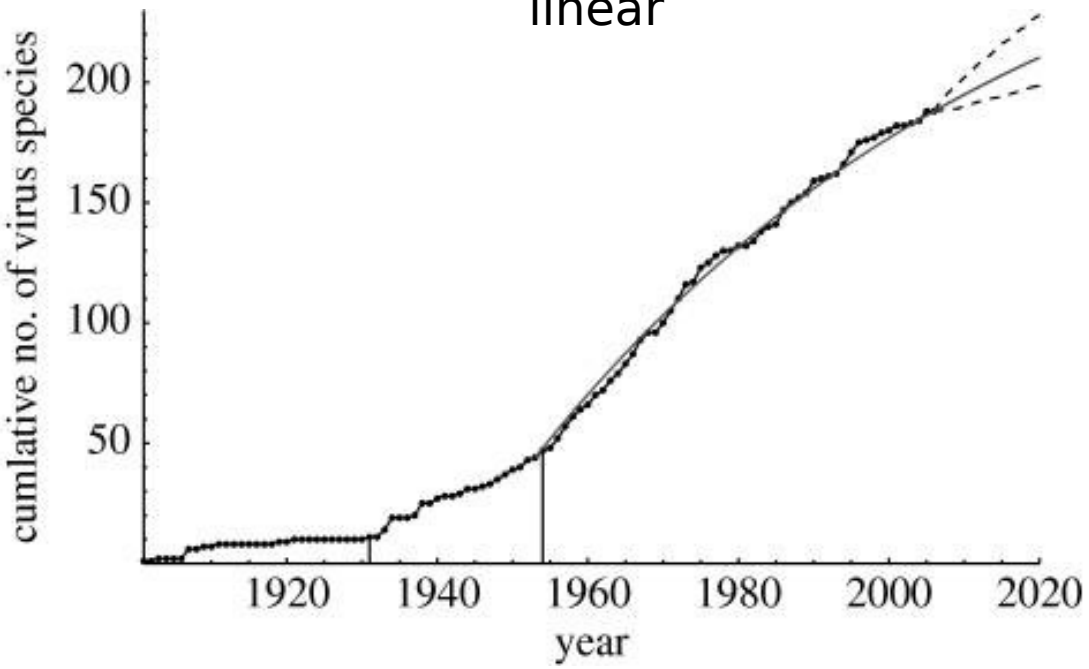
Disclosures

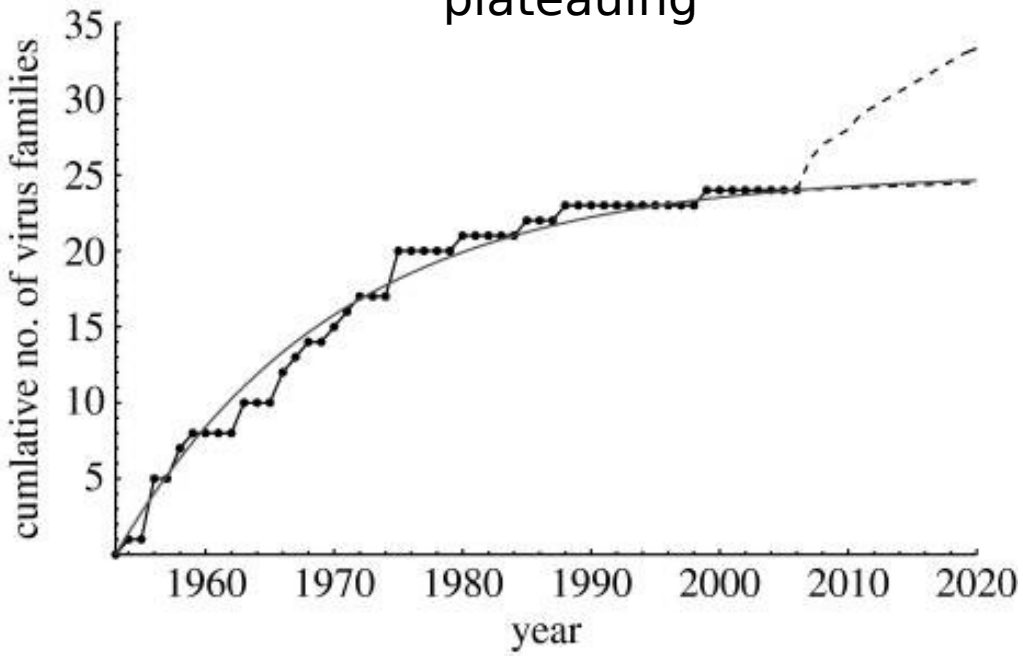
- Vaccine Inventor
  - Coronaviruses
  - Respiratory syncytial virus
  - Influenza virus
  - Nipah and other paramyxoviruses
  - Zika
- Monoclonal Antibody Inventor
  - Ebola
  - SARS-CoV-2 and other coronaviruses
- Scientific Advisory Boards
  - Icosavax
  - Vaccine Company, Inc.
  - Third Rock Ventures, Inc. Foundry
- Consultant
  - GSK
  - Pfizer
  - Janssen
  - Sanofi
  - Merck
  - AstroZeneca
  - Exevir

New Human Viral Pathogens in the 20th Century

New species
linear



New families
plateauing



Woolhouse MEJ et al Proc R Soc B 2008;
275:2111

21st Century Viral* Threats and Needs

Outbreaks

- SARS-CoV-1
- H5N1 influenza
- H1N1 influenza
- MERS
- Chikungunya
- Ebola
- Marburg
- Zika
- Nipah
- EV-D68
- SARS-CoV-2
- Monkeypox

Unsolved Problems

- HIV
- HCV
- Dengue and other flaviviruses
- Alphaviruses
- Norovirus and other nonenveloped viruses
- Bunyaviruses
- CMV and other herpesviruses
- Rapid response approach for Paramyxoviruses
- Polyomaviruses
- Other emerging infections

Could be better

- Influenza
- Mumps
- Yellow Fever
- Filoviruses

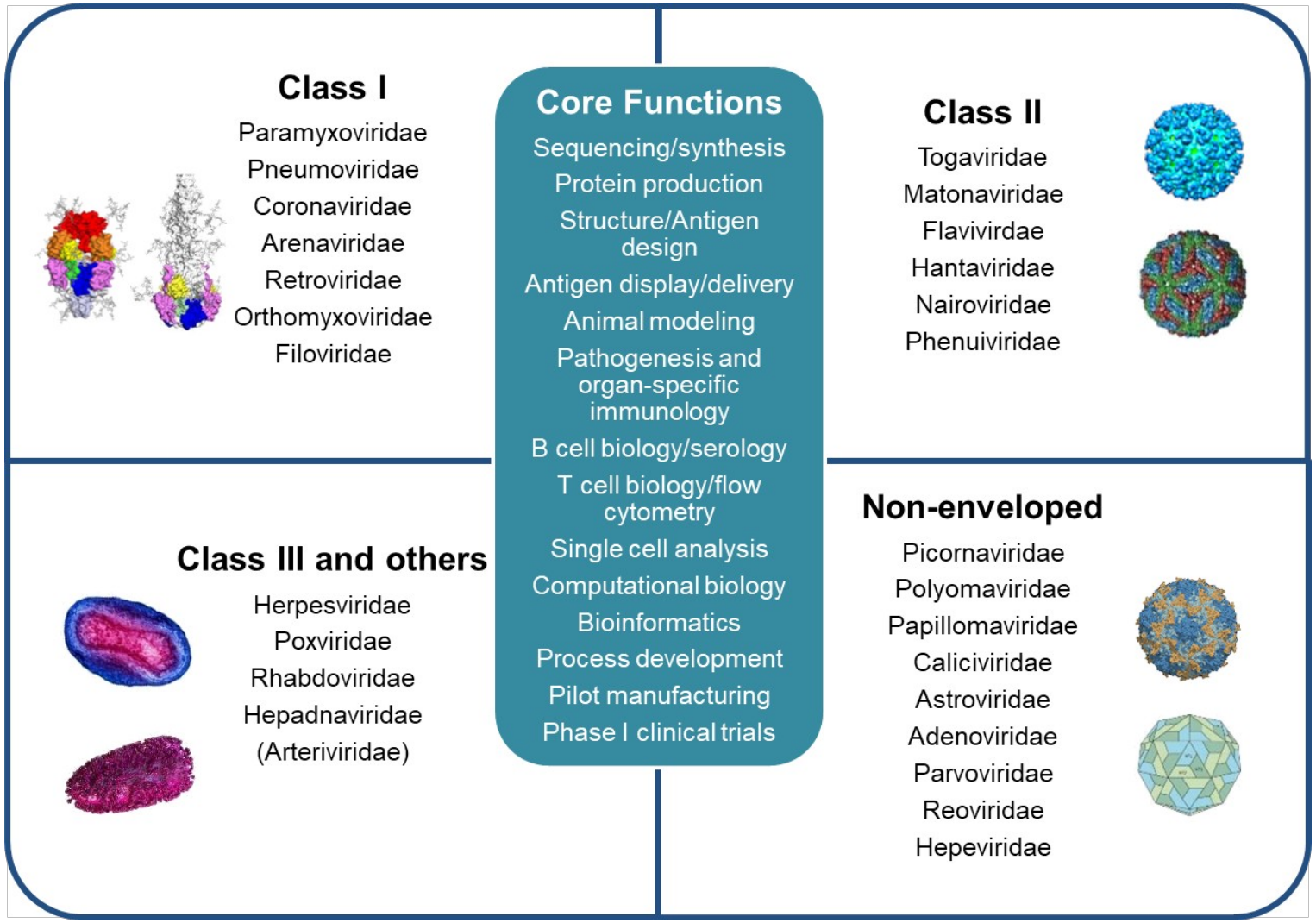
*Not to mention malaria, Tb, and all the virulent or untreatable bacteria, fungi, and parasites

Viral Taxonomy 2023

- 6 realms
- 10 kingdoms
- 17 phyla
- 2 subphyla
- 40 classes
- 72 orders
- 8 suborders
- 264 families
- 182 subfamilies
- 2818 genera
- 84 subgenera

~150 viruses from 26 families recognized as human pathogens with potential for person-to-person spread

Prototype Pathogen Approach for Pandemic Preparedness



- Pathogen biology, product development, preclinical and clinical evaluation supported by global governance and pre-established relationships with industry, regulatory authorities, and public health systems
- ~150 viruses from 26 families known to infect humans with some potential for increased human-to-human transmission and virulence
- Develop vaccines for ~30 prototype viruses through phase 1
- Develop vaccine candidates (& reagents) for other ~120 through animal testing

Graham & Sullivan. Nature Immunology 2018

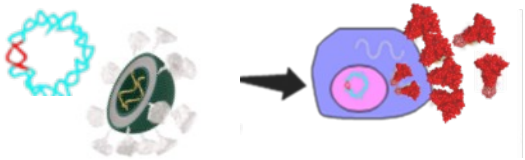
Pandemic Preparedness

- **Know what's coming**
  - Virus discovery
  - Surveillance – humans, animals, and vectors
- **Know what to do**
  - Virus characteristics including pathogenesis
  - Basis of immunity – identify antigen target
  - Antigen design and delivery
- **Know how to make biomedical countermeasures**
  - Reagents including rapid mAb identification and production
  - Diagnostics
  - Antivirals – preventive and therapeutic
  - Vaccines
  - Animal models
- **Know how to deploy interventions rapidly on a global scale**
  - Maintenance and geographic distribution of manufacturing and clinical facilities – scale-up capacity
  - Organization of governments, agencies, industry, academia, and nonprofit organizations
  - Coordination of regulatory processes and requirements
  - Communication with the public

Global COVID-19 Vaccine Landscape

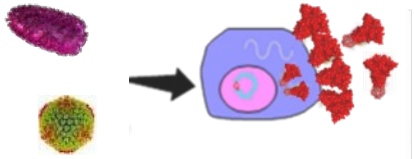
199 Vaccine Candidates in Pre-clinical Evaluation
178 Vaccine Candidates in Clinical Evaluation

Nucleic acid

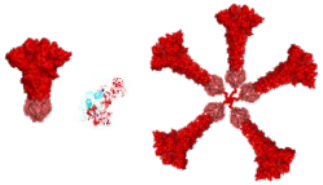


Whole-inactivated virus

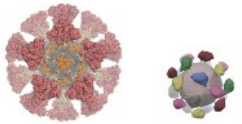
Recombinant Vectors



Recombinant proteins or subdomains



Nanoparticle display of structurally defined proteins

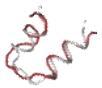


Live-attenuated virus

Recombinant or chimeric viruses

Virus-like particles

Peptides



Source: WHO 14 February 2023

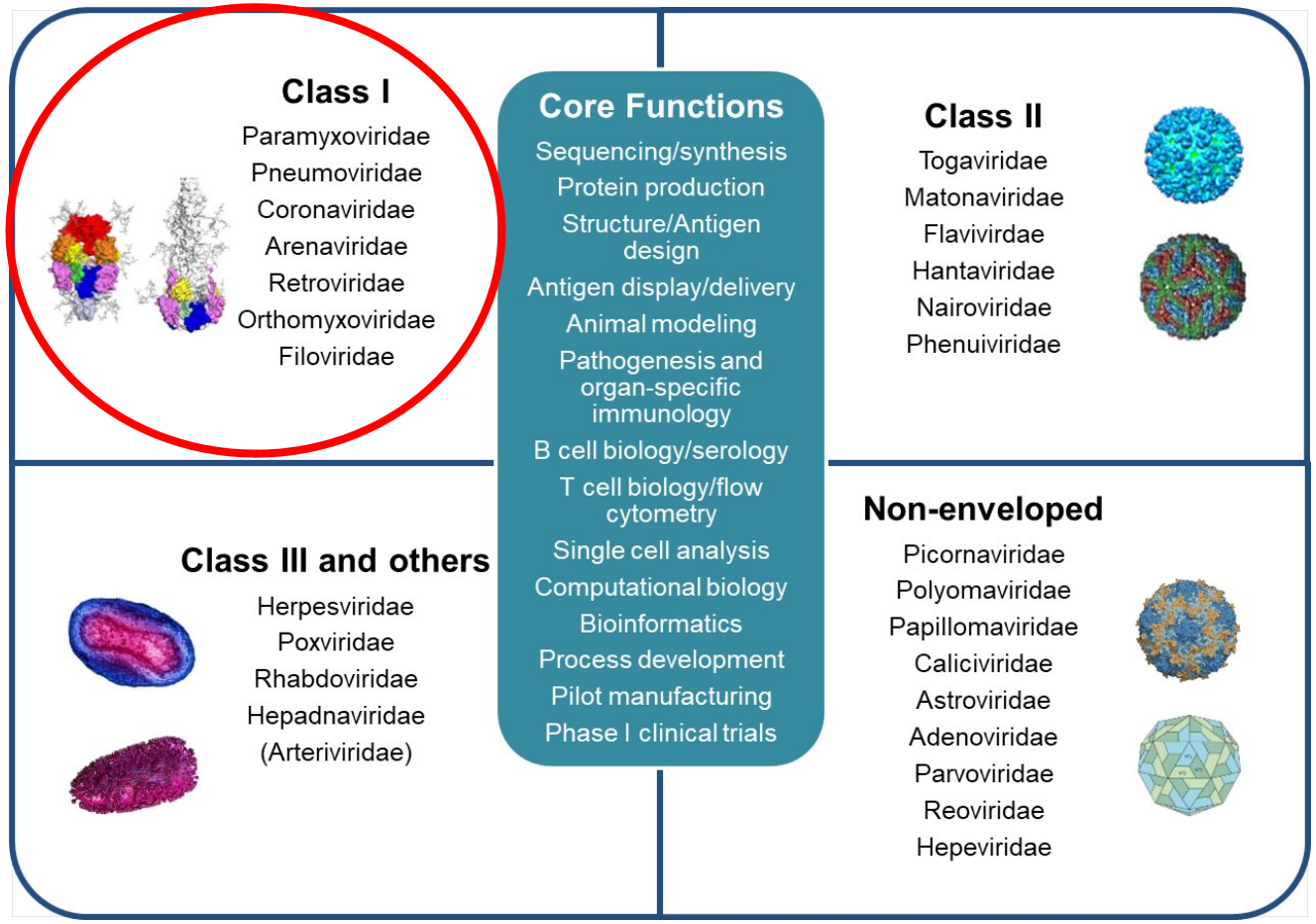
Finding Generalizable Approaches and Breakthroughs

Successes

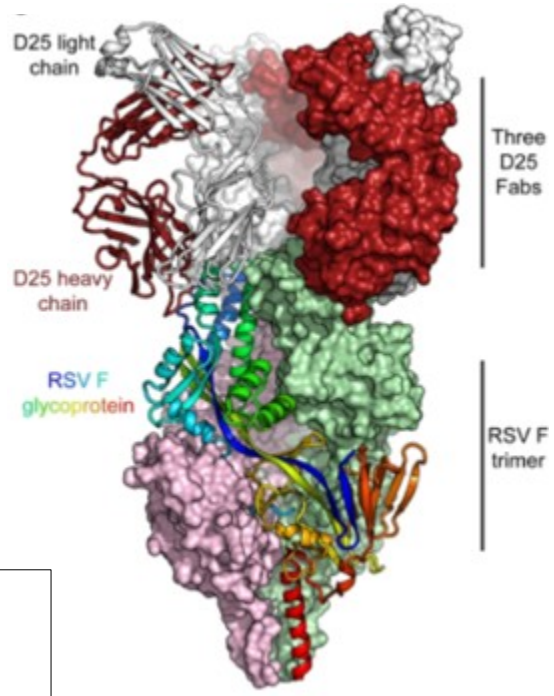
Structure-based antigen design
Self-assembling nanoparticle display
Nucleic acid, vector, or protein delivery
Single-cell analysis
Targeting antibody lineages

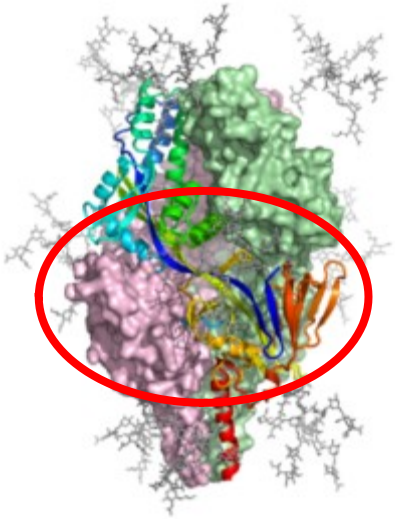
Barriers to Pandemic Preparedness

Antigenic diversity
Immunodominance
Durable responses
Mucosal immunity
Immune evasion
Potential for enhanced disease
Glycan shield
Integration and latency



Structure of Prefusion RSV F Glycoprotein



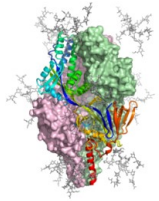


Prefusion

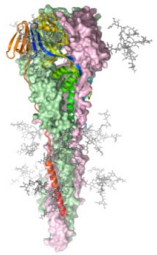
Postfusion

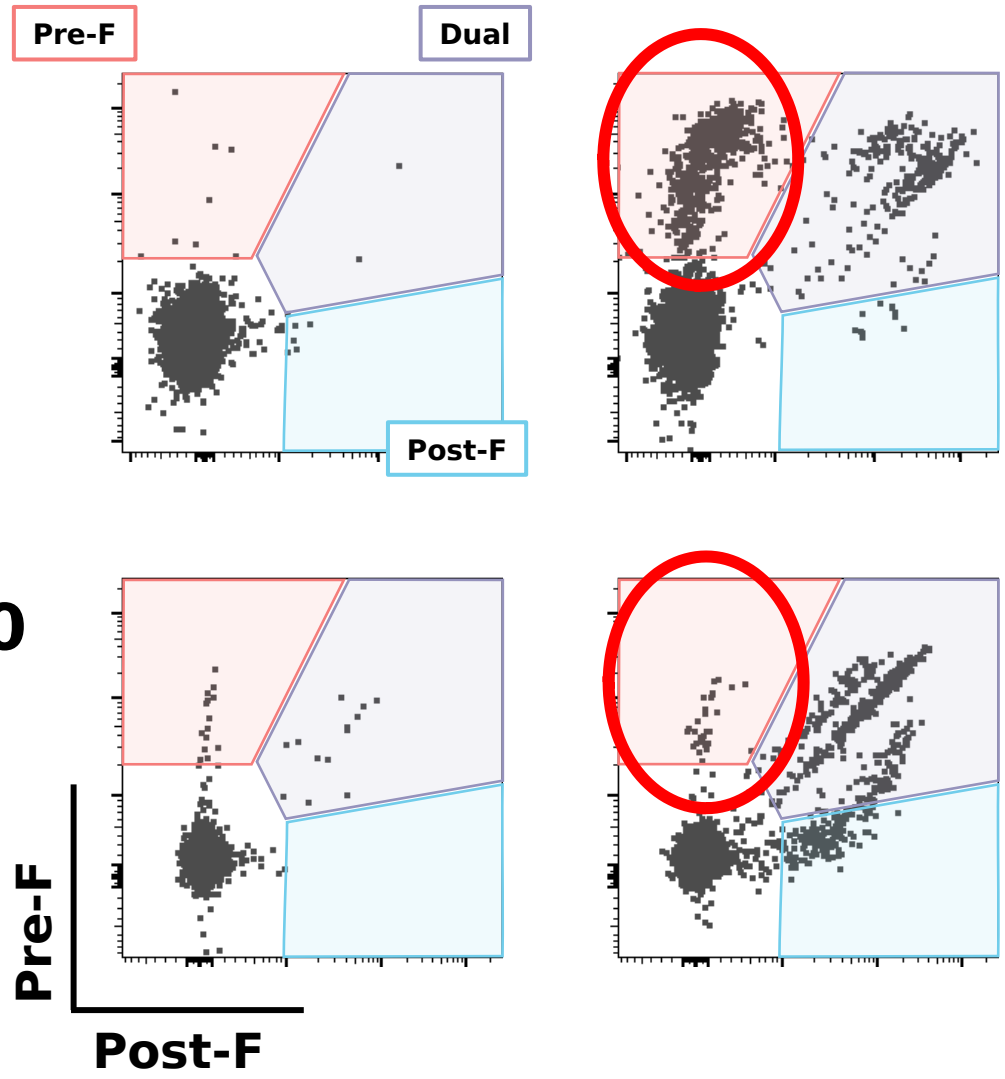
Targeting right antigenic site matters

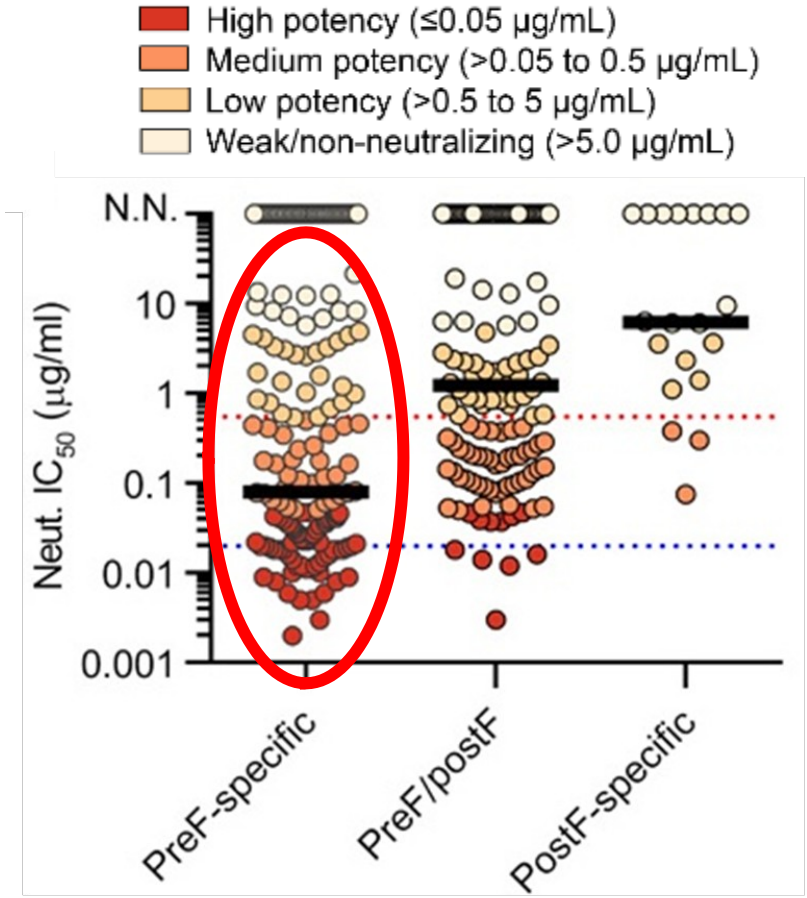
DS-Cav1 (Pre-F)



MEDI7510 (P F)



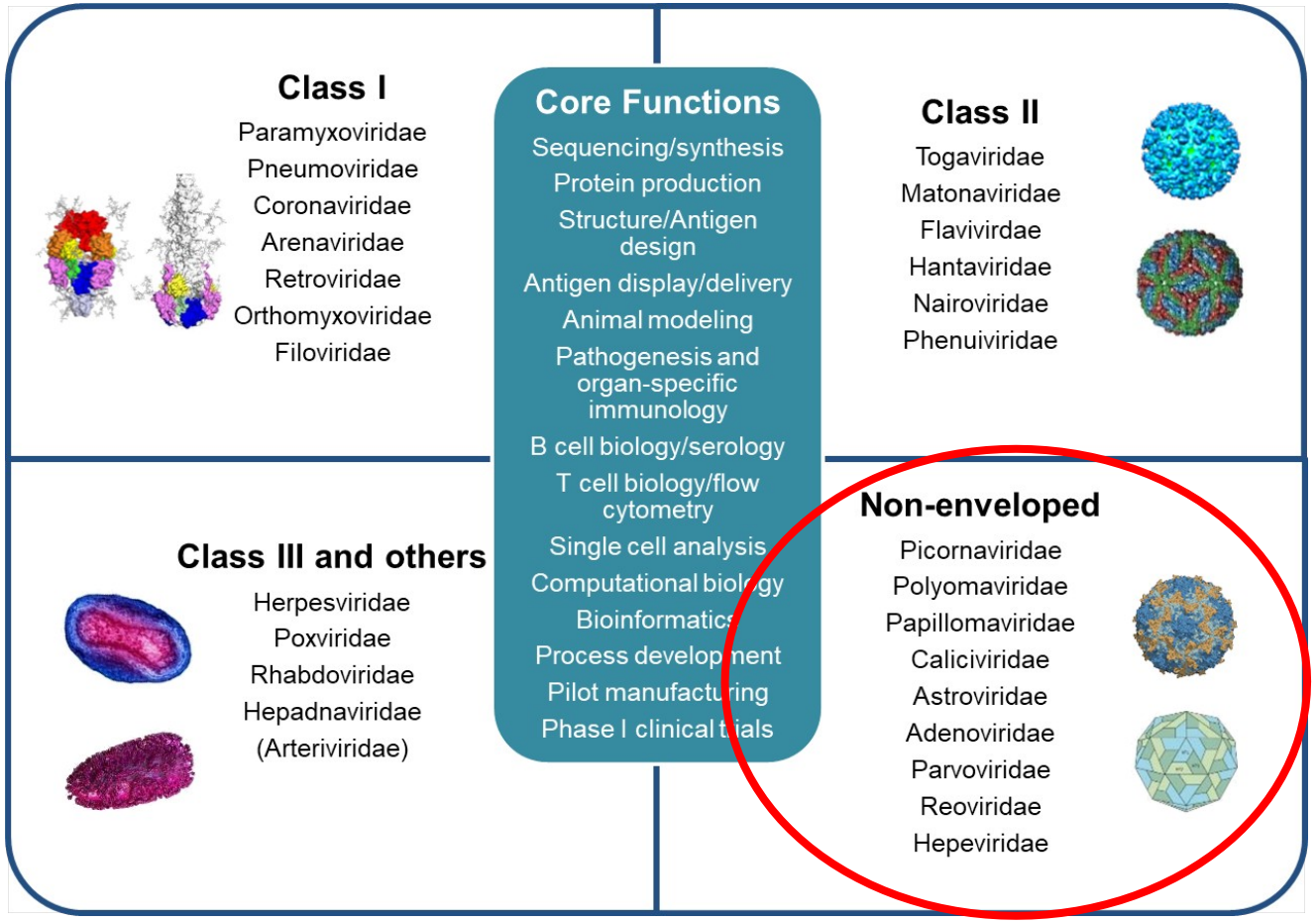




Gilman MS, et al. Rapid profiling of RSV antibody repertoires from the memory B cells of naturally infected adult donors. Sci Immunol. 2016 Dec 16;1(6):eaaj1879. doi: 10.1126/sciimmunol.aaj1879.

Emily Phung, Lauren Chang

Finding Generalizable Approaches



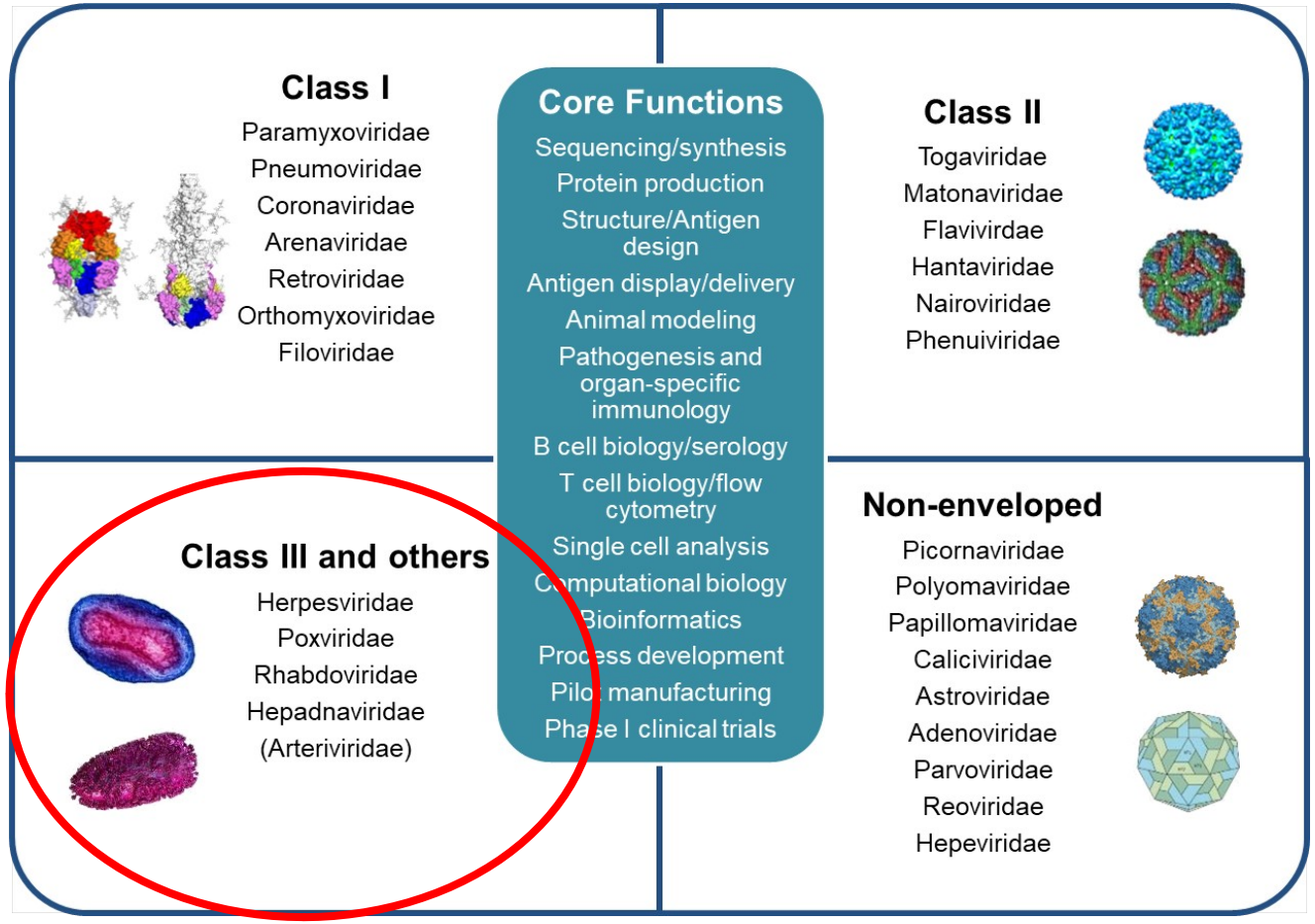
Successes
Virus-like particles
Whole-inactivated
Live-attenuated

Barriers to pandemic preparedness
Multiple serotypes
Structure and antigen definition
Mucosal immunity

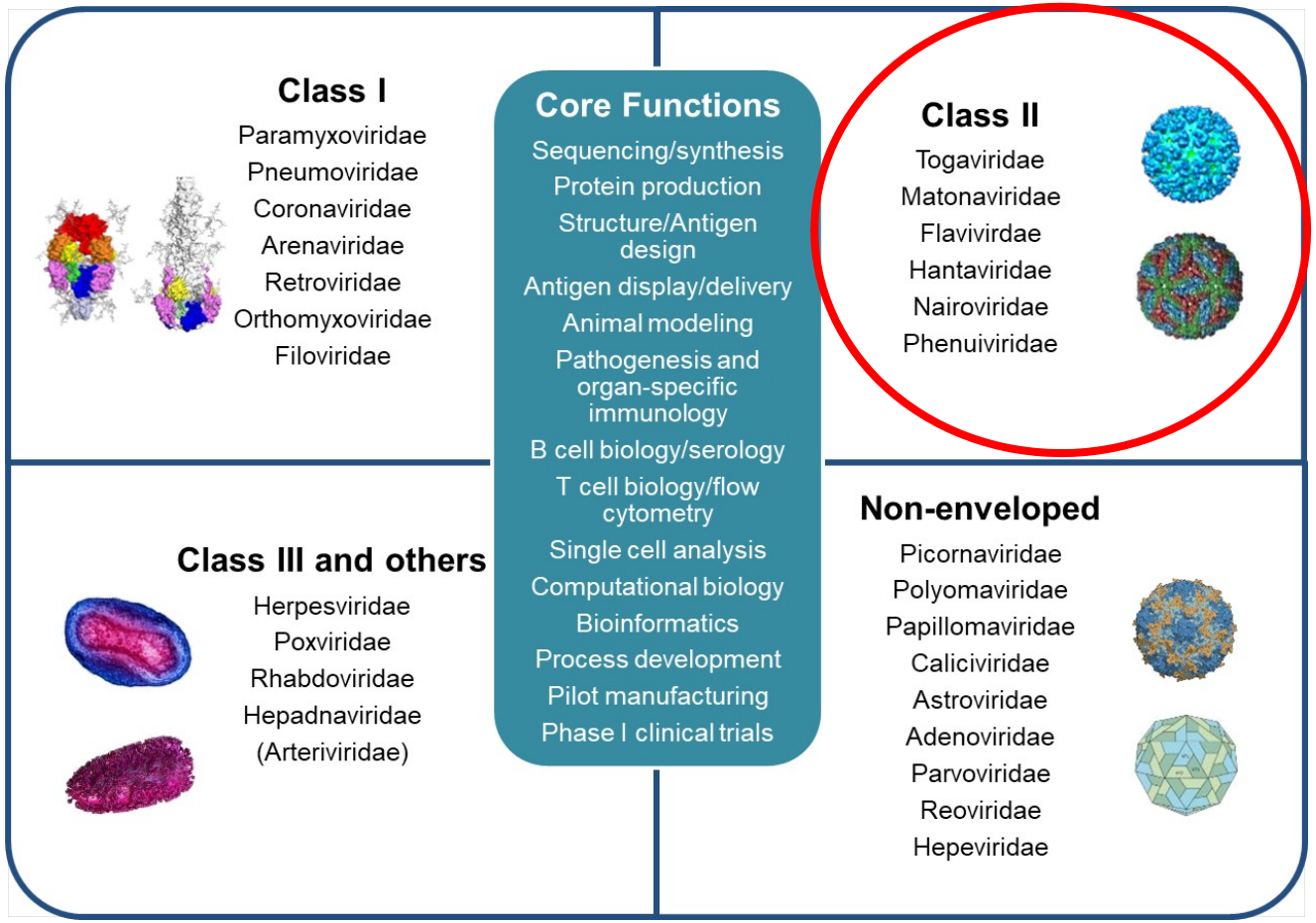
Finding Generalizable Approaches

Successes
Replication-defective virus
Live-attenuated
Protein subunit

Barriers to pandemic preparedness
Structure and antigen definition
Mucosal immunity
Integration and latency



Finding Generalizable Approaches



Successes
Live-attenuated
Virus-like particle

Barriers to pandemic preparedness
Antigen structure
Antibody-dependent enhancement

Pandemic Response

- **Early detection**
  - Sequence availability
- **Epidemiology**
  - Point of care diagnostics
  - Maintenance of public health infrastructure and reporting
- **Rapid production of fit-for-purpose products**
  - Use strain-matched antigens for vaccines
  - mAbs for diagnostics and therapy
  - Antivirals
  - Agent-specific animal models
- **Deploy**
  - Will require prior planning and agreements between governments, between agencies within governments, between governments and non-government organizations with methods of coordination and communication
  - Public-private agreements between nonprofits, philanthropists, academia, and industry

Take Home Messages

- We have the science and technology to solve most future problems but are lacking in the areas of policy and practice
- Need consensus on global coordination, communication, and governance
- Equitable distribution of basic science, translational science and manufacturing is critical to solve local problems before they become global
  - Investment in basic research
  - Surveillance needs support for prospective cohorts and sequencing facilities
  - Distributive manufacturing is feasible but needs small market business models
- Pandemic response will usually require strain-matched products